HIV Database Workshop

www.hiv.lanl.gov
seq-info@lanl.gov

Presenters: **Bette Korber, Will Fischer and Brian Foley**
Database PIs: **Bette Korber, Thomas Leitner, Karina Yusim**

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Project Officer: **Stuart Shapiro, NIAID, NIH**

Theoretical Biology and Biophysics, T-6
Los Alamos National Laboratory

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Workshop Topics

HIV Sequence Database and Immunology Database
Brian Foley, Karina Yusim

Session 2

Thursday,
March 13
11:15 – 12:30

Immunology database introduction
Epitope maps and epitope summary tables
T-cell epitope search
T-cell epitope variants
Antibody search
List of most broadly neutralizing antibodies
HIV/SIV sequence locator tool
QuickAlign – Align an epitope to the database alignments
CATNAP
ELF – epitope location finder
Peptgen – Design peptides for reagent development

Mosaic Vaccine Maker, Epicover, and Posicover
- *generate candidate vaccines*
- *estimate epitope coverage*
- *determine regional epitope coverage*

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Immunology Database Overview

- Incorporates published HIV T cell (CTL, T-helper) epitope and Antibody information (emphasis on monoclonals)
- Key information regarding what is learned about epitopes and mAbs in each paper is included
- Types of data recorded:
  - Epitope sequence and location: HXB2 numbering, subtype
  - Natural infection or vaccine
  - Host HLA or MHC
  - Ab isotype, binding region, species
  - Notes summarize main findings

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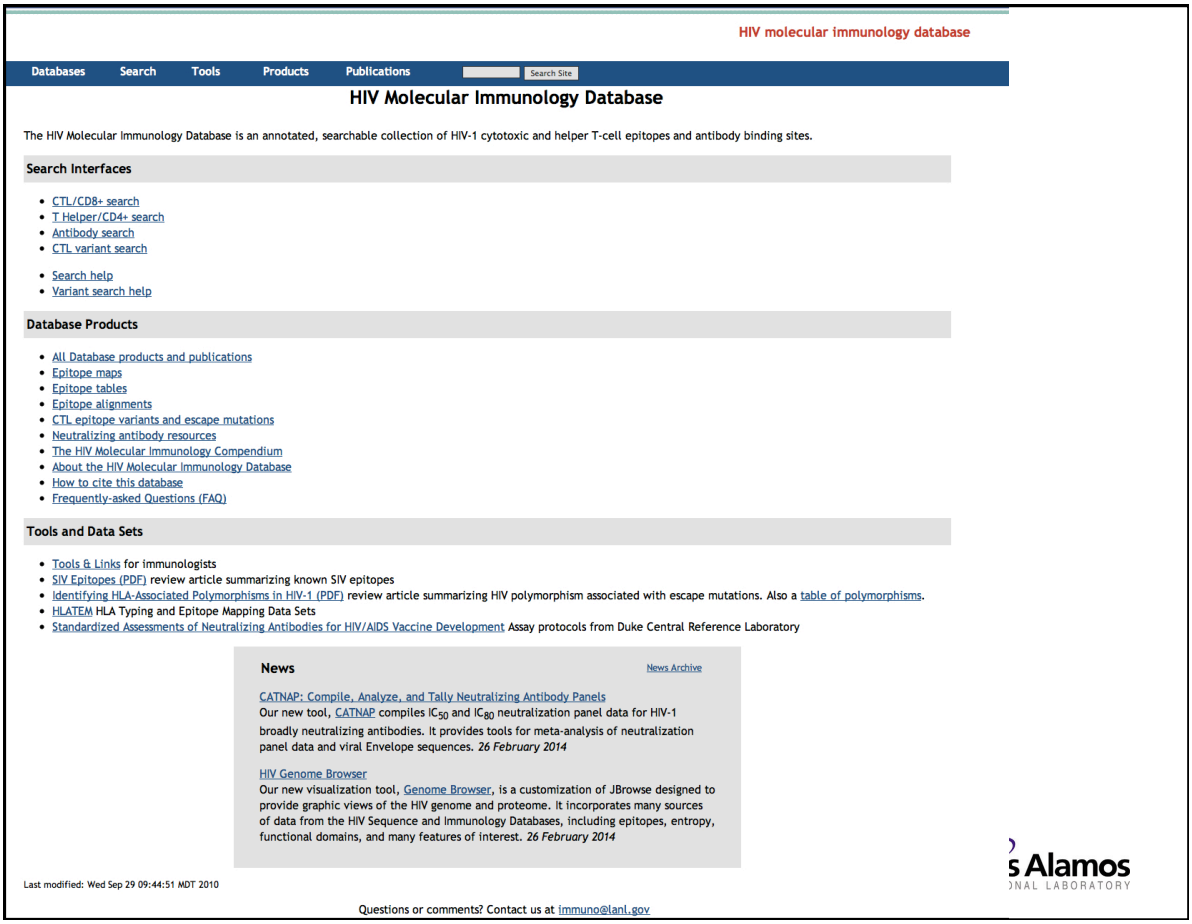

Immunology Database Products

- Epitope maps (species/HLA for T cell epitopes; species/MAb name for Ab)
- Epitope summary tables:
  - All CTL and Helper epitopes and Ab binding sites
  - Variants of CTL epitopes
  - Christian Brander keeps an “A list” of HIV CD8+ T-cell epitopes – experimentally validated optimal epitopes with known HLA presenting molecules, will be updated soon
  - “B list” – a comprehensive list of all unique epitopes in the database (unknown HLA, boundaries not fully defined…)
  - All antibodies organized by protein and binding region
  - Antibody “A-list” – a table of the most broadly neutralizing MAbs, with links to sequence and structure
- Tools for immunologists
- Yearly HIV Molecular Immunology Compendium

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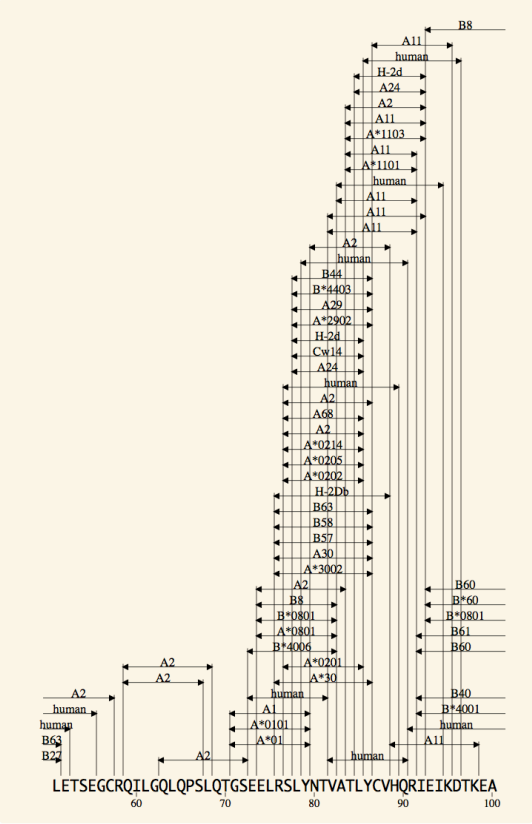
p17 CTL/CD8+ Epitope Map

- Epitopes up to 14 aa long are mapped on HXB2
- HXB2 sequence may differ
- Epitopes with identical boundaries and HLA fields are included in the maps only once
- The epitope maps are interactive!



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CTL/CD8+ Epitope Summary (B-list)

- List of all epitopes up to 21 aa long
- Unlike epitope maps that show epitope locations, here each epitope sequence is shown

Epitope	Protein	HXB2 Location	Subtype	Species	HLA
MGARASVLSG	p17	1-10	CRF01_AE	human	
ASVLSGGEL	p17	5-13	B	human	
ASILRGGKLDK	p17	5-15	C	human	
SVLSGGQLDR	p17	6-15	B	human	A11
LSGGELDRWEK	p17	8-18		macaque	
GELDRWEKI	p17	11-19	B	human	B*4002, B40
GQLDRWEKI	p17	11-19	B	human	
GKLDSWEKIRLR	p17	11-22	A, CRF01_AE, CRF02_AG	human	
GKLDAWEKIRLR	p17	11-22	CRF01_AE	human	
ELDRWEKIRL	p17	12-21	B, C	human	B63
EKIRLRPGGKKYKL	p17	17-31		human	B27, B7
KIRLRPGGK	p17	18-26	A, A1, B, CRF01_AE	human, transgenic mouse	A*0301, A11, A3, B27, B7
KIRLRPGGKK	p17	18-27	B, C, multiple	human	A*0301, A11, A3, B27
KIRLRPGGKKKYKL	p17	18-31		human	A3, B62

Best-defined CTL/CD8+ Epitope Summary (A-list)

- Selective list of best defined epitopes as described by Christian Brander and colleagues

Epitope	Protein	HXB2 Location	Subtype	Species	HLA
GELDRWEKI	p17	11-19		human	B*4002
KIRLRPGGK	p17	18-26		human	A*0301
IRLRPGGKK	p17	19-27	B	human	B*2705
RLRPGGKKK	p17	20-28		human	A*0301
RLRPGGKKKY	p17	20-29	B	human	A*0301
GGKKKYKLK	p17	24-32	B	human	B*0801
KYKLKHIVW	p17	28-36	B	human	A*2402
HLVWASREL	p17	33-41		human	Cw*0804
LVWASRELERF	p17	34-44		human	A30
WASRELERF	p17	36-44	B	human	B*3501
ELRSLYNTV	p17	74-82		human	B*0801
RSLYNTVATLY	p17	76-86	B	human	A*3002, B58, B63
SLYNTVATL	p17	77-85	B	human	A*0201, A*0202, A*0205
LYNTVATL	p17	78-85		human	Cw14
LYNTVATLY	p17	78-86		human	A*2902, B*4403
TLYCVHQK	p17	84-91		human	A*1101
IEIKDTKEAL	p17	92-101		human	B*4001
NSSKVSQNY	p17	124-132	B	human	B*3501

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Immunology Database: Search

- T Cells
  - Cytotoxic T Lymphocytes (CTL)
  - Helper T Lymphocytes (T-helper)
  - Organization is identical for CTL and T-helper
  - One reference per entry, epitope/HLA combinations are often repeated
- B Cells (Antibodies)
  - One entry for each monoclonal antibodies
  - Many references per entry (> 400 for some well studied MAbs)

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CTL/CD8+ T-cell Search

- Can search by HIV protein, Epitope Sequence, Subtype, Immunogen, Vaccine Details, Species, presenting MHC/HLA, Author, Country, Keywords
- Can now search on epitope location and find fuzzy matches, overlaps and embedded epitopes
- Search example:
  - SLYNTVATL – 254 entries
  - To narrow the search use keyword “escape” – 32 entries
- Additional information provided in the entry:
  - Location, Donor MHC/HLA, experimental methods, Notes
  - CTL epitope variants if studied in the paper
  - Link to all entries for a reference
  - PubMed links to papers
  - Link to Epitope Maps
  - Link to Epitope Alignment (Extracted from HIV-sequence database, includes subtype, country and year of sampling)

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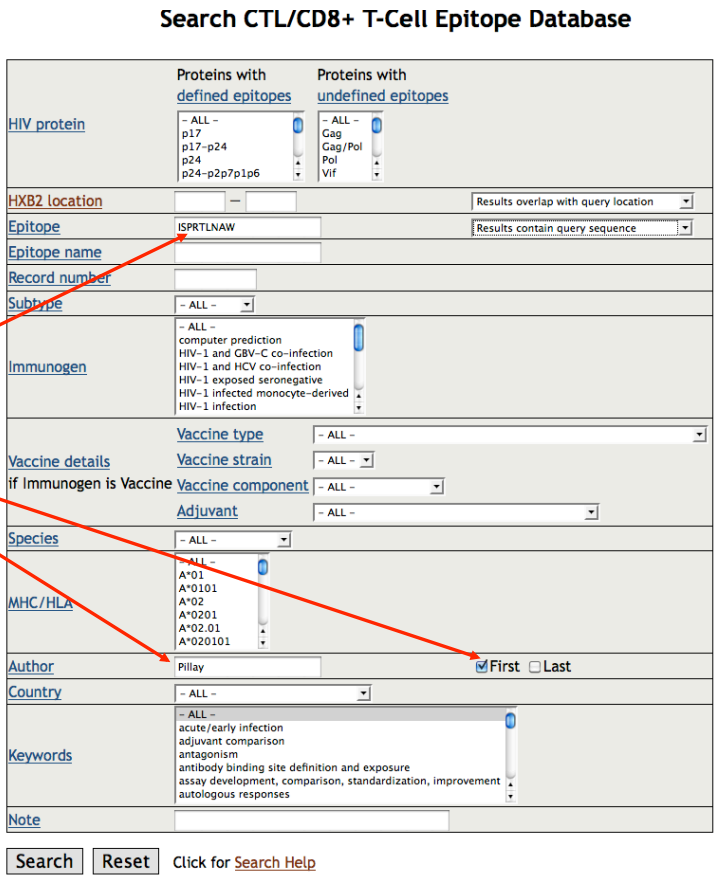
CTL/CD8+ T-cell Search

Search for

Epitope: ISPRTLNAW

First Author: Pillay



Search CTL/CD8+ T-Cell Epitope Database

Found 1 matching record:

Displaying record number 53832

HXB2 Location	p24(15-23)	p24 Epitope Map
Author Location	Gag(147-155)	
Epitope	ISPRTLNAW	Epitope Alignment
		Show epitope variants
Subtype	C	
Species (MHC/HLA)	human(B57)	
Immunogen	HIV-1 infection	
Donor MHC/HLA	A*3001, A*66, B*4201, B*5802, Cw*0602, Cw*1701; A*66, A*68, B*57, B*5802, Cw*0602, Cw*0701	
Country	South Africa	
Experimental methods	CD8 T-cell Elispot - IFNy	
Keywords	epitope processing, responses in children, mother-to-infant transmission, escape, acute/early infection	

Variant details with annotator's notes

Notes

- HIV-specific CTLs in infants were shown to be able to select for viral escape variants early in life, despite a lack of escape with the same CTL specificity in the mother. Infant CTL responses may be compromised by transmission of escape variants that arose in the mother and also those that arose in the father, if the father was the source of the mother's infection.
- ISPRTLNAW is the C consensus form of the epitope and was the autologous form in the mother, and was transmitted to her infant. By 33 weeks a new dominant form of the epitope had emerged in the infant, mSPRTLNAW, and two additional variants had arisen, one with a substitution proximal to the epitope, plSPRTLNAW, and lSPRTLNAW.

References

Pillay2005 Thillagavathie Pillay, Hua-Tang Zhang, Jan W. Drijfhout, Nicola Robinson, Helen Brown, Munira Khan, Jagadesa Moodley, Miriam Adhikari, Katja Pfafferott, Margaret E. Feeney, Anne St. John, Edward C. Holmes, Hoosen M. Coovadia, Paul Klenerman, Philip J. R. Goulder, and Rodney E. Phillips. Unique Acquisition of Cytotoxic T-Lymphocyte Escape Mutants in Infant Human Immunodeficiency

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Variants details

Displaying record number 53832

HXB2 Location	p24(15-23)	p24 Epitope Map
Epitope	ISPRTLNAW	Epitope Alignment
	mSPRTLNAW	escape documented in this paper
Variants	lSPRTLNAW	diminished response
	plISPRTLNAW	not determined
Species (MHC/HLA)	human(B57)	

Can go back to epitope entry

Variant Details

Showing all 3 variants.

Variant ID.	1413
Epitope Seq.	ISPRTLNAW
Variant Seq.	mSPRTLNAW
Mutations	I/M
Epitope Location	I1M
HXB2 Location	I15M
Mutation Type	**E**: escape documented in this paper
Method	CD8 T-cell Elispot - IFNy, Sequence
Note	This is de novo variant seen in infant by week 33 of age. The index peptide was recognized, but not the variant.

Mutation type

Note describing why the variant was designated particular mutation type

Variant ID.	1414
Epitope Seq.	ISPRTLNAW
Variant Seq.	lSPRTLNAW
Mutations	I/L
Epitope Location	I1L
HXB2 Location	I15L
Mutation Type	**DR**: diminished response
Method	CD8 T-cell Elispot - IFNy, Sequence

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Summary table of ~ 2800 epitope variants

CTL/CD8+ Epitope Variant Details

Download CTL/CD8+ epitope variant details as CSV or XLS files.

List of Mutation types

Data last updated at 2013-01-25 11:58:16-07

Epitope ID	Epitope Name	Variant ID	Subtype	Epitope Subtype	Variant Subtype	Protein	HXB2 start	HXB2 end	HLA	Epitope	Variant Epitope	Mutation (epitope)	Mutation (protein)	Mutation Type Code	Mutation Type Description	Methods	Note	References
54532	Al14	1016	B	B	A, M-group	p17	5	19		ASVLSGGELDRWEKI	ASVLSGGkLDaWEKI	R11A, E8K	R15A, E12K	SNSF	subtype-specific non-susceptible form	CD8 T-cell Elispot - IFNγ	No cross-recognition of this variant was seen across clades or intra-clade central sequences.	Malhotra2007
54532	Al14	1017	B	B	C	p17	5	19		ASVLSGGELDRWEKI	ASILrGGkLDkWEKI	R11K, V3I, S5R, E8K	R15K, V7I, S9R, E12K	SNSF	subtype-specific non-susceptible form	CD8 T-cell Elispot - IFNγ	No cross-recognition of this variant was seen across clades or intra-clade central sequences.	Malhotra2007
54532	Al14	1018	B	B	B	p17	5	19		ASVLSGGELDRWEKI	ASVLSGGkLDkWEKI	R11K, E8K	R15K, E12K	SNSF	subtype-specific non-susceptible form	CD8 T-cell Elispot - IFNγ	No cross-recognition of this variant was seen across clades or intra-clade central sequences.	Malhotra2007
54532	Al14	1019	B	B	B	p17	5	19		ASVLSGGELDRWEKI	ASVLSGGELDkWEKI	R11K	R15K	SNSF	subtype-specific non-susceptible form	CD8 T-cell Elispot - IFNγ	No cross-recognition of this variant was seen across clades or intra-clade central sequences.	Malhotra2007
53591	Gag 1.2	54		B	CRF02_AG	p17	8	18		LSGGELDRWEK	LSGGkLDaWEK	E5K, R8A	E12K, R15A	SNSF	subtype-specific non-susceptible form	Intracellular cytokine staining, T-cell Elispot	CRF02 form, LSGGkLDaWEK, does not cross-react with the B clade LSGGELDRWEK elicited response.	Amara2005a
53844	GI9	1569	B			p17	11	19	B40	GELDRWEKI	GELDRWkKI	E7K	E17K	DR, LE	diminished response, literature escape	CD8 T-cell Elispot - IFNγ, Sequence	This variant from the HXB2 sequence was present in the restricting HLA-B40-carrying mother, M-1002, but was never detected in her non-HLA-B40-carrying infant, P-1031. Decreased recognition of the E17K variant relative to the index epitope was seen in the mother.	Sanchez-Merino2005
56027	GI9(p17)	1903	B	B	B	p17	11	19		GQLDRWEKI	GeLDRWEKI	Q2E	Q12E	ND	not determined	CD8 T-cell Elispot - IFNγ, Sequence	This Asian B Clade optimal epitope differs from the consensus B at one position. It is predicted to be HLA-B40 restricted. Experimentally, B clade consensus peptide was used to challenge CTL response in subjects commonly carrying the Asian B-type epitope.	Zhai2008
55632		11	A, CRF02_AG, CRF01_AE	A, AG	AE	p17	11	22		GKLDSWEKIRLR	GKLDaWEKIRLR	S5A	S15A	SSF	subtype-specific susceptible form	CD8 T-cell Elispot - IFNγ	1 subject responded to peptide GKLDSWEKIRLR from subtypes CRF02_AG and A and to peptide GKLDaWEKIRLR from subtype CRF01_AE.	Aidoo2008
54629	GAG-03	1957	B	B	C	p17	17	34		EKIRLRPGGKKKYRLKHL	EKIRLRPGGKkhYmLKHL	K12H, R14M	K28H, R30M	SSF	subtype-specific susceptible form	CD8 T-cell Elispot - IFNγ, Sequence	This Clade C consensus synthetic peptide variant from an immunodominant region, differs from the immunodominant Clade B consensus at 2 amino acids (11.1%) and both were recognized by subtype-B-infected subjects.	Zhao2007
53201	KK9	31	B			p17	18	26	A3	KIRLRPGGK	KIRLRPGGq	K9Q	K26Q	E, P	escape documented in this paper, processing	CD8 T-cell Elispot - IFNγ, Flow cytometric T-cell cytokine assay	Variant inhibits processing, resulting in rapid decline in the KK9 specific CD8+ T-cell response.	Allen2004
55770	KK9	153	B			p17	18	26	A3	KIRLRPGGK	KIRLRPGGr	K9R	K26R	SF	susceptible form	Flow cytometric T-cell cytokine assay	KIRLRPGGK was recognized by 3 patients. The autologous sequence in one patient was KIRLRPGGr which induced high frequency response.	Daucher2008
55233		790	B, CRF01_AE		B	p17	18	26	A3	KIRLRPGGK	KIRLRPGGr	K9R	K26R	IE	inferred escape	Sequence	Patient was superinfected with three strains, B1, B2 and CRF01_AE. This variant developed in B1 to include 42% of the viruses within 4 years.	Kozaczynska2007

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Antibody Search

- Can search by
  - HIV protein, Epitope Sequence, Subtype, Immunogen, Vaccine Details, Species, presenting MHC/HLA, Author, Country, Keywords
  - MAb ID (Ab lists by name and by binding type are provided)
  - Ab type (by binding site, for example binding to similar region like V3 or near a common functional domain like CD4 binding site CD4Bs)
  - Isotype
- Search examples:
  - 2F5 – 1 record with 463 references
  - Ab type: gp120 CD4BS – 200 records

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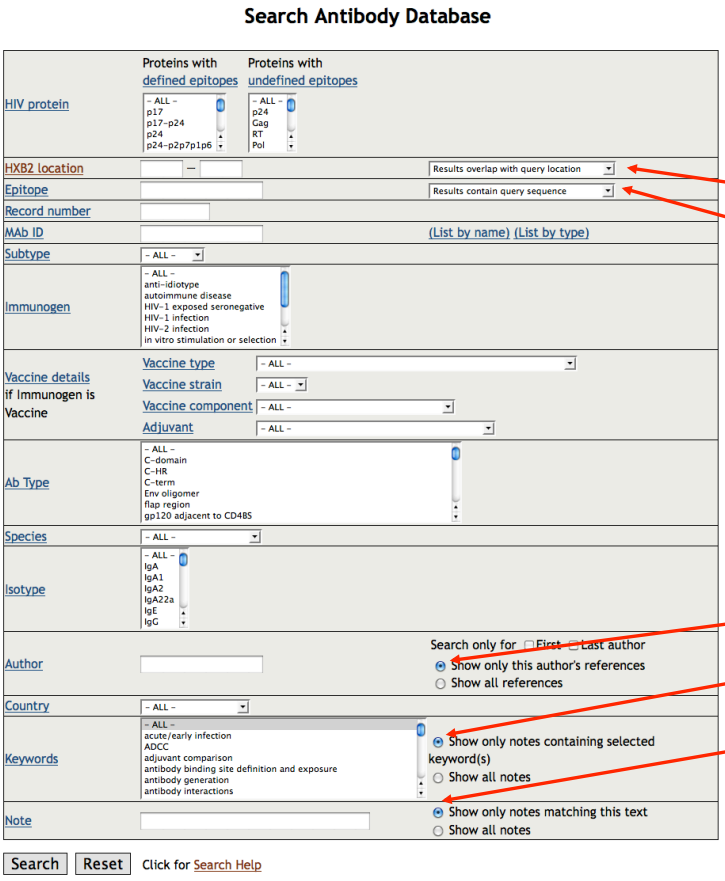
Antibody Search



Can search by HXB2 location, Find overlaps, fuzzy matches Embedded epitopes

Can show only notes and references containing selected keywords or user's text (as apposed to showing matching Ab entries with all notes)

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Antibody Search

Found 1 matching record:

Displaying record number 815

MAb ID	2F5 (IAM 2F5, IAM-41-2F5, IAM2F5, c2F5)	
HXB2 Location	gp160(662-667)	gp160 Epitope Map
Author Location	gp41(662-667 BH10)	
Research Contact	Hermann Katinger, Institute of Applied Microbiology, Vienna, or Polymun Scientific Inc., Vienna, Austria	
Epitope	ELDKWA	Epitope Alignment
Ab Type	gp41 adjacent to cluster II, C-term, gp41 MPER (membrane proximal external region)	
Neutralizing	L P	
Species (Isotype)	human(IgG3κ)	
Immunogen	HIV-1 infection	
Keywords	acute/early infection, adjuvant comparison, anti-idiotype, antibody binding site definition and exposure, antibody generation, antibody interactions, antibody sequence variable domain, assay development, standardization and improvement, autoantibody or autoimmunity, autologous responses, binding affinity, brain/CSF, co-receptor, complement, dendritic cells, drug resistance, enhancing activity, escape, genital and mucosal immunity, HAART, ART, HIV exposed persistently seronegative (HEPS), immunoprophylaxis, immunotherapy, immunotoxin, isotype switch, kinetics, mimics, mimotopes, mother-to-infant transmission, neutralization, rate of progression, responses in children, review, SIV, structure, subtype comparisons, supervised treatment interruptions (STI), therapeutic vaccine, vaccine antigen design, vaccine-induced immune responses, variant cross-recognition or cross-neutralization, viral fitness and reversion	

Notes

- 2F5: 2F5 neutralized infection of PBLs with various HIV-1 strains with high potency. However, 2F5 did not inhibit transcytosis of cell-free or cell-associated virus across a monolayer of epithelial cells. A mixture of 13 MAbs directed to well-defined epitopes of the HIV-1 envelope, including 2F5, did not inhibit HIV-1 transcytosis, indicating that envelope epitopes involved in neutralization are not involved in mediating HIV-1 transcytosis. When the mixture of 13 MAbs and HIV-1 was incubated with polyclonal anti-human γ chain, the transcytosis was partially inhibited, indicating that agglutination of viral particles at the apical surface of cells may be critical for HIV transcytosis inhibition by HIV-specific Abs. *Chomont2008* (**neutralization**)
- 2F5: The lipid binding properties of 2F5, and the similarity to binding properties of anti-lipid mAbs, are discussed. Potential role of liposomes containing lipid A for induction of NAbs to lipids of HIV-1 is reviewed. *Alving2008* (**autoantibody or autoimmunity, review**)
- 2F5: A reference panel of recently transmitted Tier 2 HIV-1 subtype B envelope viruses was developed representing a broad spectrum of genetic diversity and neutralization sensitivity. The panel includes viruses derived from male-to-male, female-to-male, and male-to-female sexual transmissions, and CCR5 as well as CXCR4 using viruses. The envelopes displayed varying degrees of neutralization sensitivity to 2F5, with 14 of 19 enevlopes sensitive to neutralization by this Ab. *Schweighardt2007* (**assay development, standardization and improvement, neutralization**)
- 2F5: This review summarizes data on possible vaccine targets for elicitation of neutralizing Abs and discusses whether it is more practical to design

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Antibody "A-list"

- List of most broadly neutralizing antibodies – currently 45 MAbs (*work in progress*)
  - Links to papers, Ab sequences and structures
  - Notes on breadth of neutralization
  - Notes on Ab contact residues
  - Notes on heavy and light chain composition

- Under "Database products"

- http://www.hiv.lanl.gov/content/immunology/tables/ab_best_neutralizing_summary.html

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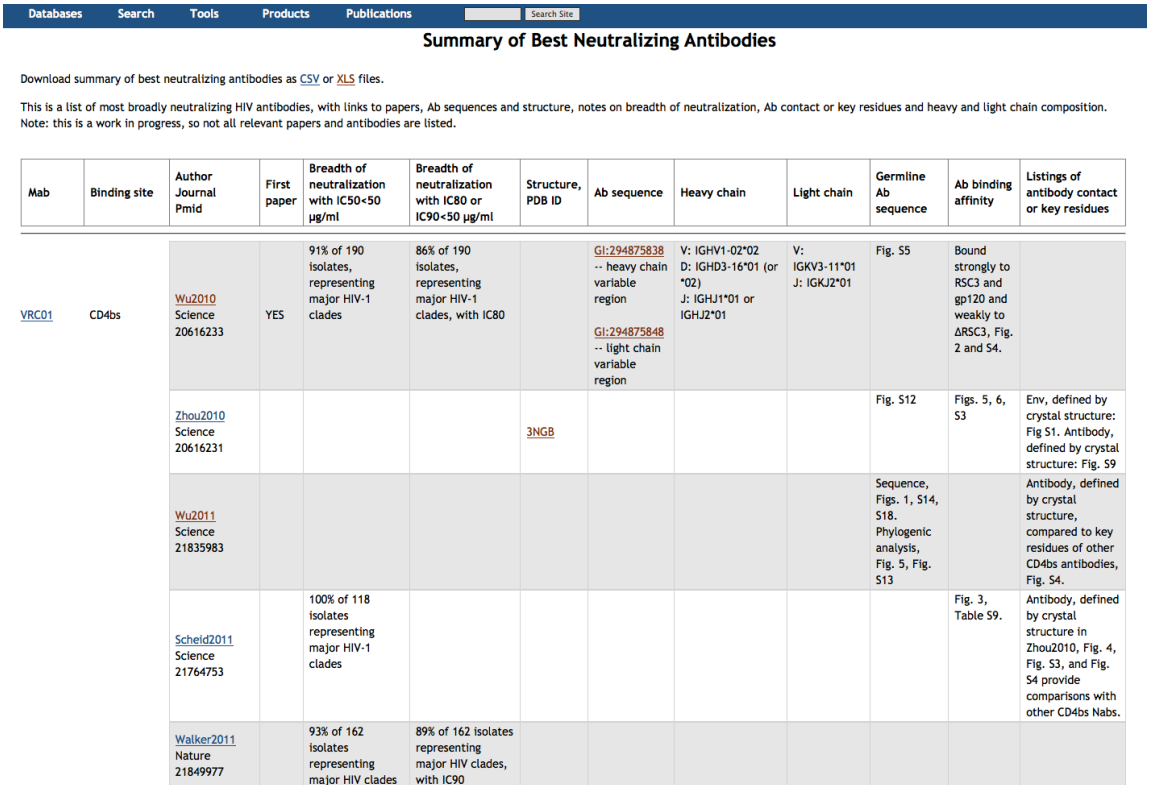

Databases Search Tools Products Publications Search Site

Summary of Best Neutralizing Antibodies

Download summary of best neutralizing antibodies as CSV or XLS files.

This is a list of most broadly neutralizing HIV antibodies, with links to papers, Ab sequences and structure, notes on breadth of neutralization, Ab contact or key residues and heavy and light chain composition.
Note: this is a work in progress, so not all relevant papers and antibodies are listed.

Mab	Binding site	Author Journal Pmid	First paper	Breadth of neutralization with IC50<50 µg/ml	Breadth of neutralization with IC80 or IC90<50 µg/ml	Structure, PDB ID	Ab sequence	Heavy chain	Light chain	Germline Ab sequence	Ab binding affinity	Listings of antibody contact or key residues
VRC01	CD4bs	Wu2010 Science 20616233	YES	91% of 190 isolates, representing major HIV-1 clades	86% of 190 isolates, representing major HIV-1 clades, with IC80		GI:294875838 -- heavy chain variable region GI:294875848 -- light chain variable region	V: IGHV1-02*02 D: IGHD3-16*01 (or *02) J: IGHJ1*01 or IGHJ2*01	V: IGKV3-11*01 J: IGKJ2*01	Fig. S5	Bound strongly to RSC3 and gp120 and weakly to ΔRSC3, Fig. 2 and S4.	
		Zhou2010 Science 20616231				3NGB				Fig. S12	Figs. 5, 6, S3	Env, defined by crystal structure: Fig S1. Antibody, defined by crystal structure: Fig. S9
		Wu2011 Science 21835983								Sequence, Figs. 1, S14, S18. Phylogenic analysis, Fig. 5, Fig. S13		Antibody, defined by crystal structure, compared to key residues of other CD4bs antibodies, Fig. S4.
		Scheid2011 Science 21764753		100% of 118 isolates representing major HIV-1 clades							Fig. 3, Table S9.	Antibody, defined by crystal structure in Zhou2010, Fig. 4, Fig. S3, and Fig. S4 provide comparisons with other CD4bs Nabs.
		Walker2011 Nature 21849977		93% of 162 isolates representing major HIV clades	89% of 162 isolates representing major HIV clades, with IC90							

http://www.hiv.lanl.gov/content/immunology/tables/ab_best_neutralizing_summary.html
Epitope Summary Tables
Best Neutralizing Antibodies

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Tools for Immunologists

- **Sequence Locator** Finds epitope location on the reference genome
- **QuickAlign** Aligns amino acids or nucleotides against our alignments
- **PeptGen** Generates overlapping peptides for any protein
- **CATNAP**: Compile, Analyze and Tally NAb Panels
- **ELF** Epitope Location Finder
- **N-Glycosite** Finds N-linked glycosylation sites
- **Mosaic** Generates candidate vaccine protein cocktails
- **Heatmaps** Displays and organizes neutralization or other quantitative data.
- And more …

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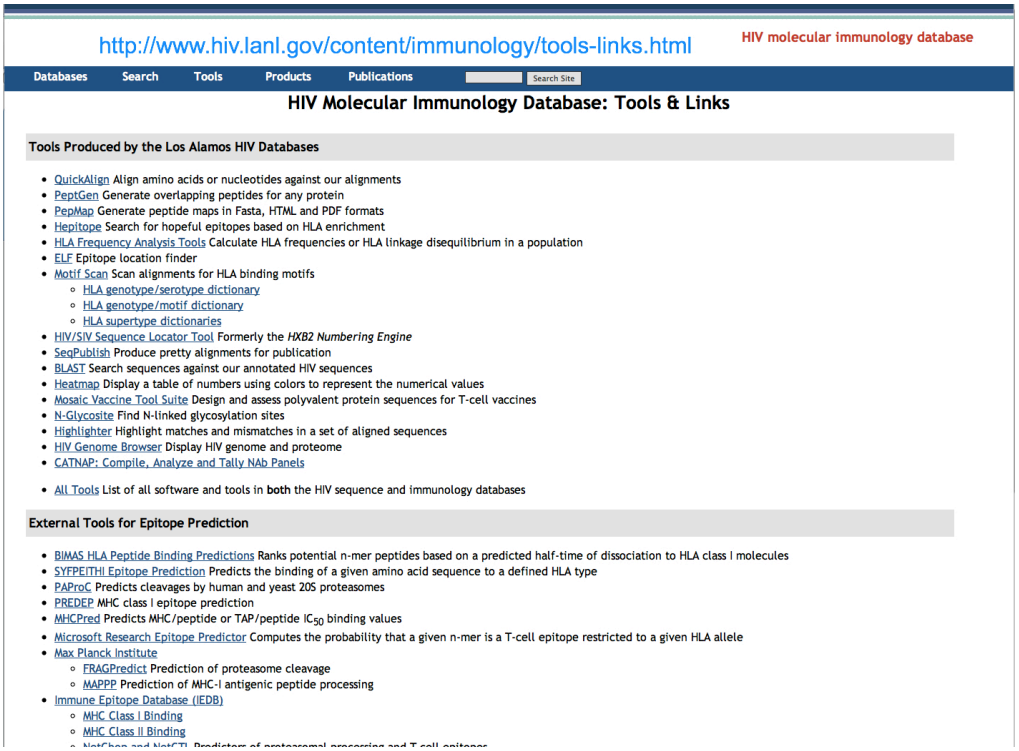

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HIV/SIV Sequence Locator Tool

- Instantly computes position numbers of DNA or protein fragments relative to a reference strain (HXB2r for HIV-1, SMM239 for SIV)
  - Such numbers, often included in the literature, are frequently incorrect
- Shows the location of the sequence on an HIV map
- Presents protein translations of DNA sequences
- Can be used for input into the search interface, to align a new sequence you have generated with the database set
- Can also retrieve reference sequences
  - by coordinates (range of base or amino-acid positions)
  - by single position (retrieves flanking sequences)

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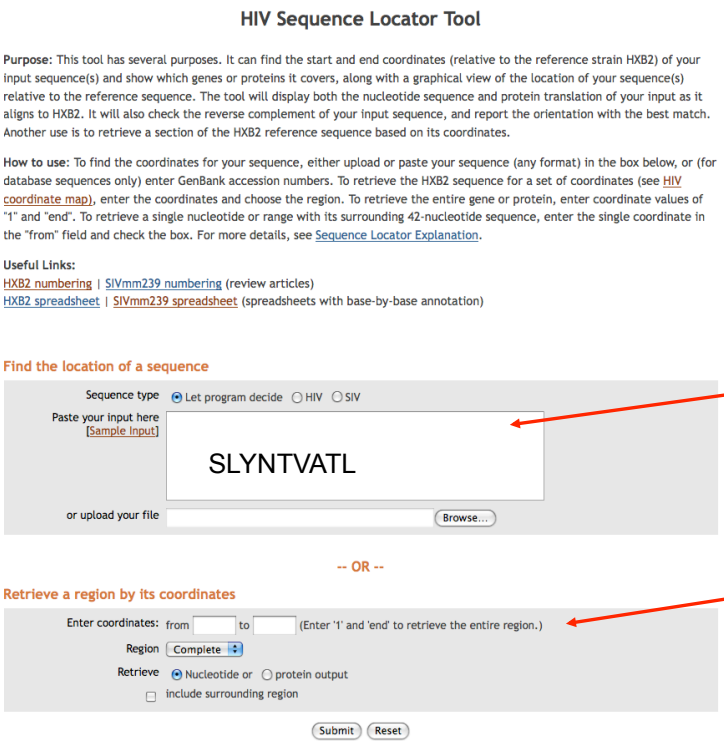
http://www.hiv.lanl.gov/content/sequence/LOCATE/locate.html



Paste or type a DNA or protein sequence here.

OR enter numeric coordiantes here.

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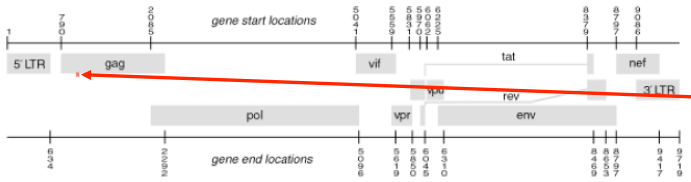
Sequence Locator: "find my sequence"

Result for SLYNTVATL Query sequence



Location in genome mapped in red.

Table of protein regions touched by query sequence. AA = amino acid, NA = nucleic acid.

CDS	AA position relative to protein start in HXB2	AA position relative to query sequence start	AA position relative to polyprotein start in HXB2	NA position relative to CDS start in HXB2	NA position relative to HXB2 genome start
Gag	77 → 85	1 → 9	NA	229 → 255	1018 → 1044
p17	77 → 85	1 → 9	NA	229 → 255	1018 → 1044

Numeric coordinates useful for entry on search form

Alignment of the query sequence to HXB2 (Similarity 100.0%):

```
Query SLYNTVATL  9
      :::::::::
 HXB2 SLYNTVATL
```

DNA and protein sequence displayed

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Sequence Locator: "Retrieve from coordinates"

-- OR --

Retrieve a region by its coordinates

Enter coordinates: from 77 to 85 (Enter '1' and 'end' to retrieve the entire region.)

Region: Gag

Retrieve: ○ Nucleotide or ◉ protein output

☐ include surrounding region

Submit Reset

Include surrounding region

Reference Strain	Type	Region	Start	End
HXB2	pro	complete	77	85

Retrieved Sequence:

SLYNTVATL

Reference Strain	Type	Region	Start	End
HXB2	pro	complete	56	106

Retrieved Sequence:

GCRQILGQLQPSLQTGSEELRSLYNTVATLYCVHQRIEIKDTKEALDKIEE

50 aa long stretch

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QuickAlign

- Generates an alignment of your HIV-1 amino acid or nucleotide sequence against our web alignments
- Can be used to align epitopes, functional domains, or any protein or nucleotide region of interest
- Calculates frequency of variants to the query sequence and summarizes both by subtype and all subtypes together
- Calculates frequency of amino acid or nucleotide by position and summarizes both by subtype and all subtypes together

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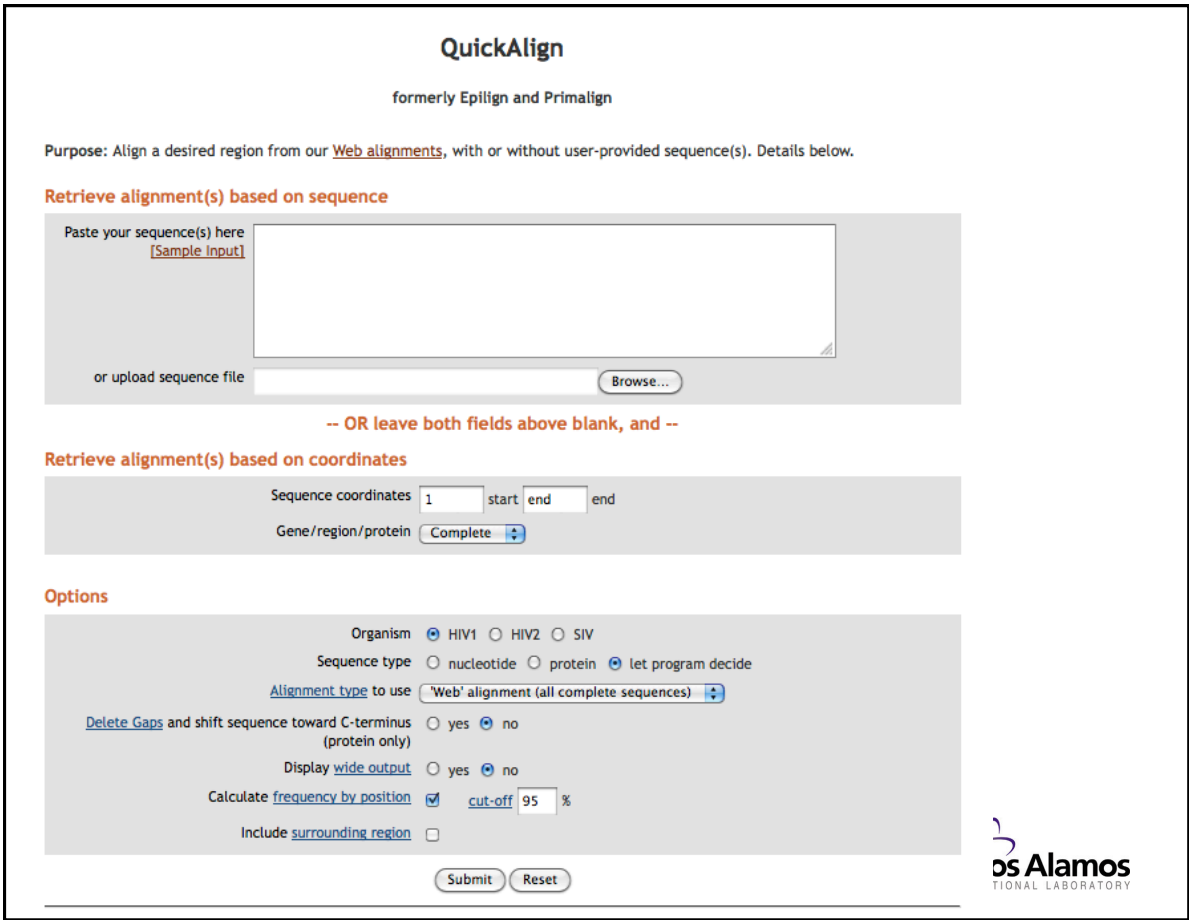

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QuickAlign: example of output

- Query peptide: SLYNTVATL
- Sequence names include subtype, country and year of sampling
- Identical sequences are shown in red

Query:	SLYNTVATL
Query Length:	9
HXB2 Location:	Gag 77-85 = p17 77-85
Alignment:	GAG, 458 sequences

Summarize

```
Query                SLYNTVATL
A1.KE.86.ML170       --F------
A1.KE.94.Q23         --F------
A1.SE.94.SE7253      --F----V-
A1.SE.94.SE7535      ---------
A1.SE.95.SE8538      ---------
A1.SE.95.SE8891      ---------
A1.SE.95.UGSE8131    ---------
A1.TZ.97.97TZ03      --F----V-
```

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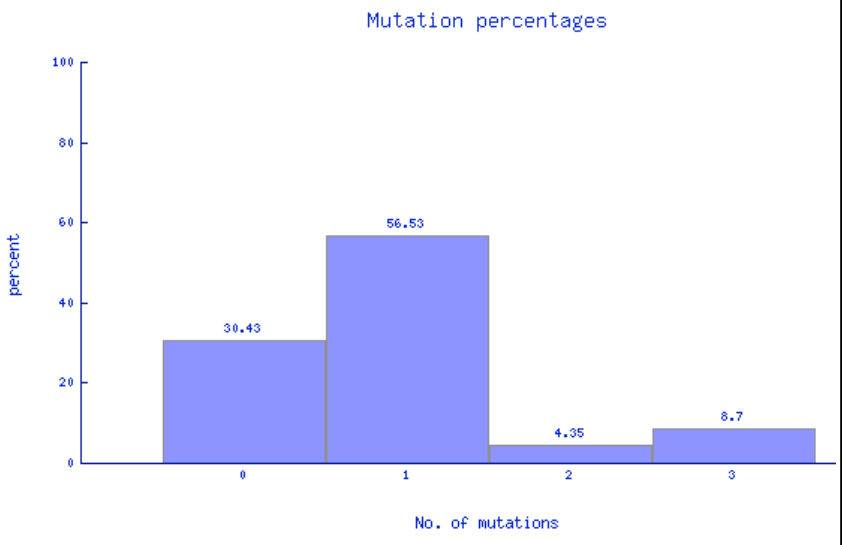
QuickAlign: sequence variant summary

Summary for subtype A

Variant	Count	Percent
SLYNTVATL		
--F------	11	47.83
---------	7	30.43
--F--I-V-	1	4.35
--F----V-	1	4.35
-------V-	1	4.35
----L----	1	4.35
--F-A--V-	1	4.35

Total sequences = 23
Number of variants = 7



- Variant frequency summary by subtype and all subtype together

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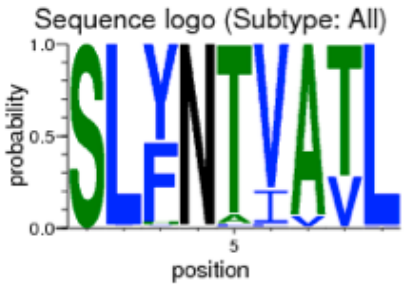
QuickAlign:
Frequency by position

Frequency by position — Go to top

See full raw counts — cutoff: 95%

Position	Percentage and raw count of non-gap	Non-gap/total (percentage)
1	S: 99.90% (3113) other: 0.10% (3)	3116/3119 (100.00%)
2	L: 98.90% (3068) other: 1.10% (34)	3102/3119 (99.55%)
3	Y: 52.71% (1633) F: 43.77% (1356) other: 3.52% (109)	3098/3119 (99.42%)
4	N: 99.68% (3104) other: 0.32% (10)	3114/3119 (99.94%)
5	T: 92.86% (2887) A: 5.05% (157) other: 2.09% (65)	3109/3119 (99.78%)
6	V: 79.35% (2448) I: 18.15% (560) other: 2.50% (77)	3085/3119 (99.01%)
7	A: 92.95% (2889) V: 6.53% (203) other: 0.51% (16)	3108/3119 (99.74%)
8	T: 72.52% (2254) V: 27.06% (841) other: 0.42% (13)	3108/3119 (99.74%)
9	L: 99.00% (3078) other: 1.00% (31)	3109/3119 (99.78%)



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Neutralizing Abs: state of the field

- Despite 30 years of research, there is no HIV-1 vaccine, but recent developments offer a new hope for a protective immunization with neutralizing capacity
- In addition to the overall genetic variability and recombination events, HIV-1 Env spike escapes neutralizing antibody response through indels, hyper-variable loops, extensive glycosylation and conformational masking of vulnerable epitopes
- Only 4 (and not very potent or broad) cross-reactive neutralizing MAbs were known for more than 20 years of HIV-1 research
- During last 5 years several dozens of potent and broad NAbs were isolated, based on
  - New highly accurate neutralization assays and panels of 100s of diverse HIV isolates
  - New techniques to screen sera from many HIV-infected individuals to find elite neutralizers and clone Abs from their B cells
  - Novel Ab selection, screening and isolation approaches, including PCR amplification from single B-cells, structure-guided Env bait design, new PCR primers to target more conserved regions of immunoglobulin genes, next generation sequencing etc.
- The results of large neutralization panels can allow powerful meta-analyses to find antibody neutralization signatures and sites of vulnerability
- Most studies do not supply sufficient HIV sequence information: large Env panels are published without accession numbers, with a huge discrepancy in sequence names, making subsequent signature analysis of even one study difficult, let alone multiple studies
- The neutralization panels published as PDF tables, difficult to use

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HIV molecular immunology database

Databases | Search | Tools | Products | Publications | Search Site

Neutralizing Antibody Resources

Tools

- CATNAP: Compile, Analyze and Tally NAb Panels
  Meta-analysis of neutralization panels for HIV-1 neutralizing antibodies.
- HIV Genome Browser
  A customization of jBrowse displaying genome and proteome features of HIV, including epitopes and neutralizing antibody features.

Search interface

- Neutralizing antibody contexts and features
  Search for locations of important neutralizing antibody binding sites and other HIV-1 Env features.

Tables

- Neutralizing antibody contexts and features (.xls)
  A summary of the information from the search interface above, presented in a single .xls spreadsheet. Each row of the table corresponds to one residue of HIV-1 Env, and each column represents a protein feature or set of known binding residues of broadly neutralizing antibodies. Loops and other features of Env are shown in the first 3 columns on the left. The entropy (sequence variability) of each residue is presented numerically and color coded. Abbreviated references are listed under each column heading, and full references are on the second page of the Excel file.
- Best neutralizing antibodies
  A table presenting the most broadly-neutralizing HIV-1 antibodies, with links to papers, Ab sequences, structures, notes on breadth of neutralization, locations of Ab contacts or key residues, and heavy and light chain composition.

Last modified: Wed Sep 29 09:44:51 MDT 2010

Questions or comments? Contact us at immuno@lanl.gov

CATNAP

Compile, Analyze and Tally NAb Panels

CATNAP:
Theoretical approximation …

By Peter Hraber

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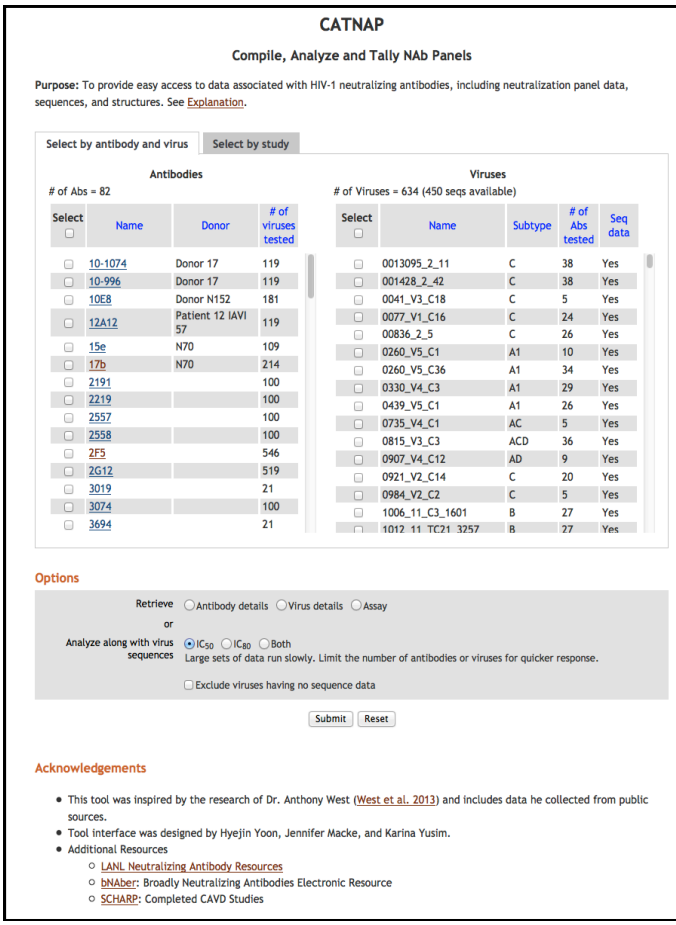

- Inspired by Anthony West (*West et al, PNAS 2013*) and includes data he collected from published sources
- Designed by Hyejin Yoon, Jennifer Macke, Bette Korber, Karina Yusim

Interface combines:

- Antibody-virus neutralization data
  - Env sequence data superimposed with IC50 or IC80 values
  - Antibody potency and breadth summarized over multiple studies
- Alignments and virus data
  - Subtype, country, accession, neutralization tier, virus names
  - Patient health status, risk factor
- Antibody data
  - Isolation study, donor ID, clonal lineage, Immuno DB records
  - PDB structure, Ab sequences
  - Neutralizing antibody features, contexts and contact residues
- Analysis per AA position
  - AA composition, N-glycosylation sites, basic statistics
  - What is known about this position in terms of entropy, functional domain, neutralizing antibody contexts, Ab contacts and signature predictions

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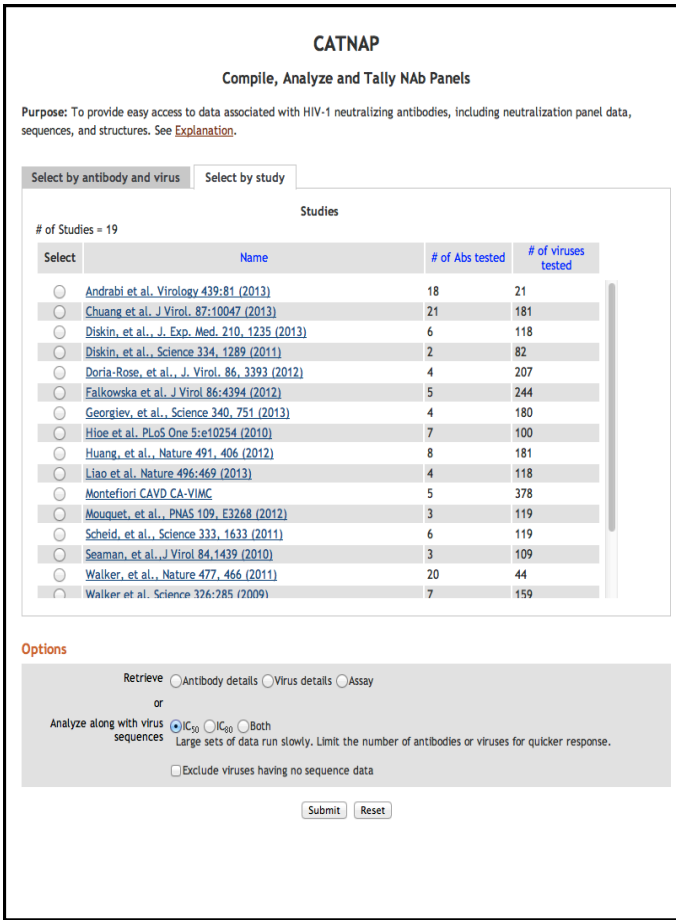

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- Analysis per AA position
  - AA composition, N-glycosylation sites, basic statistics
  - What is known about this position in terms of entropy, functional domain, neutralizing antibody contexts, Ab contacts and signature predictions

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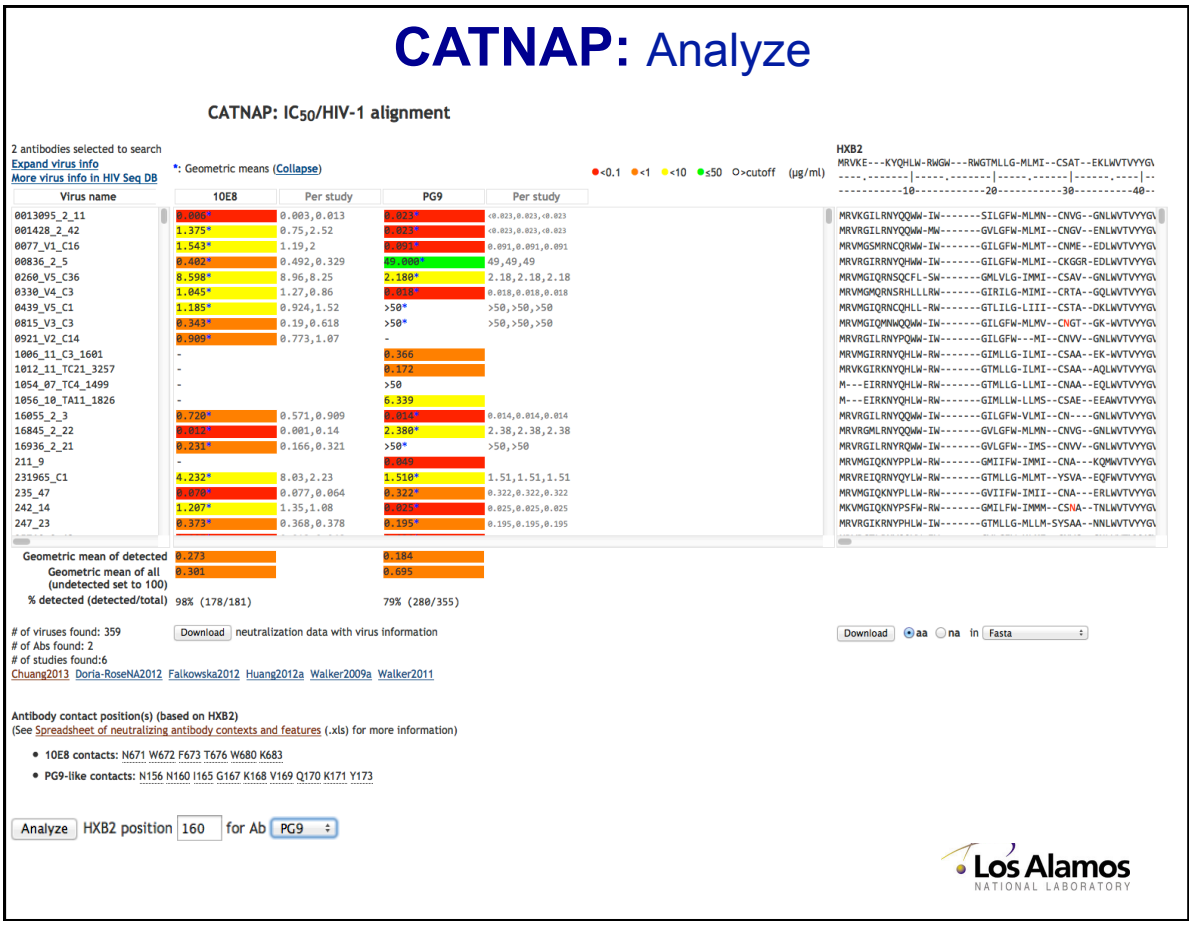
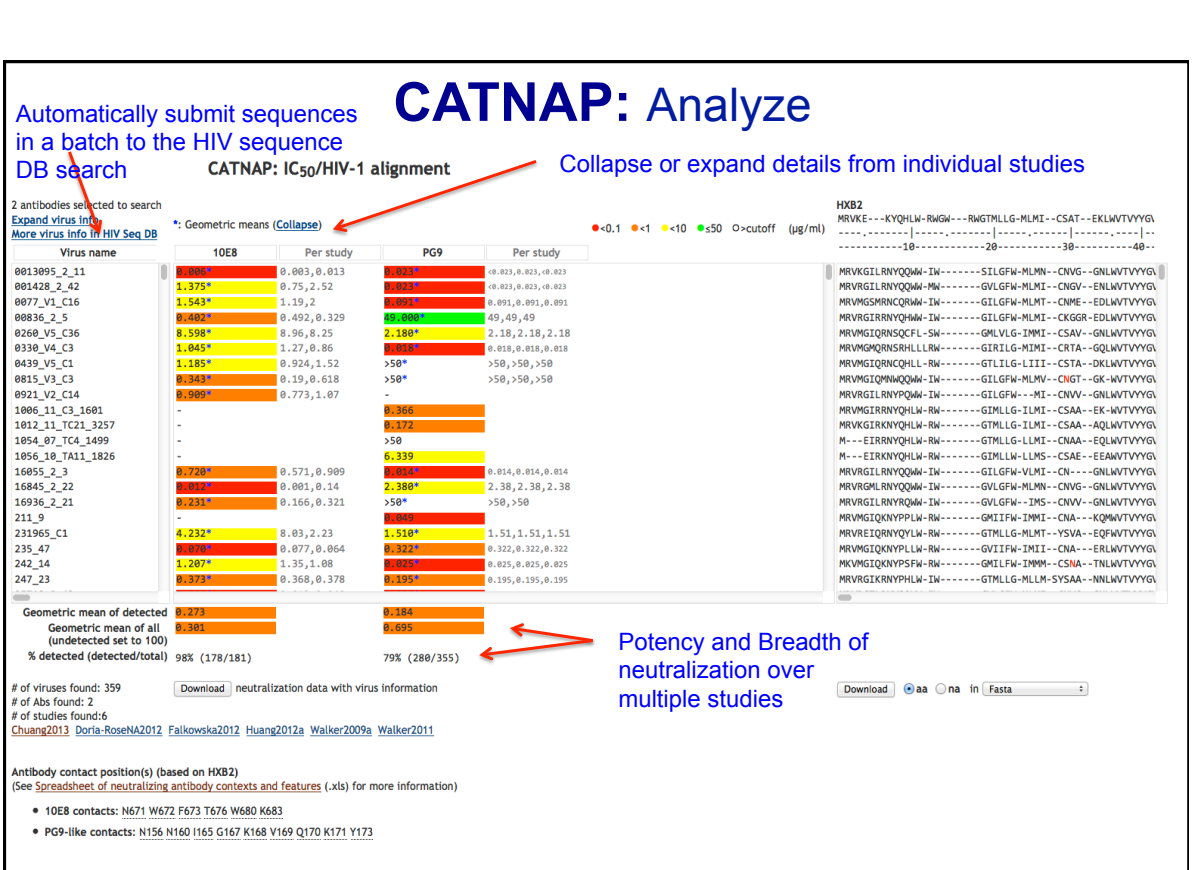
CATNAP: Analyze



CATNAP: Analyze

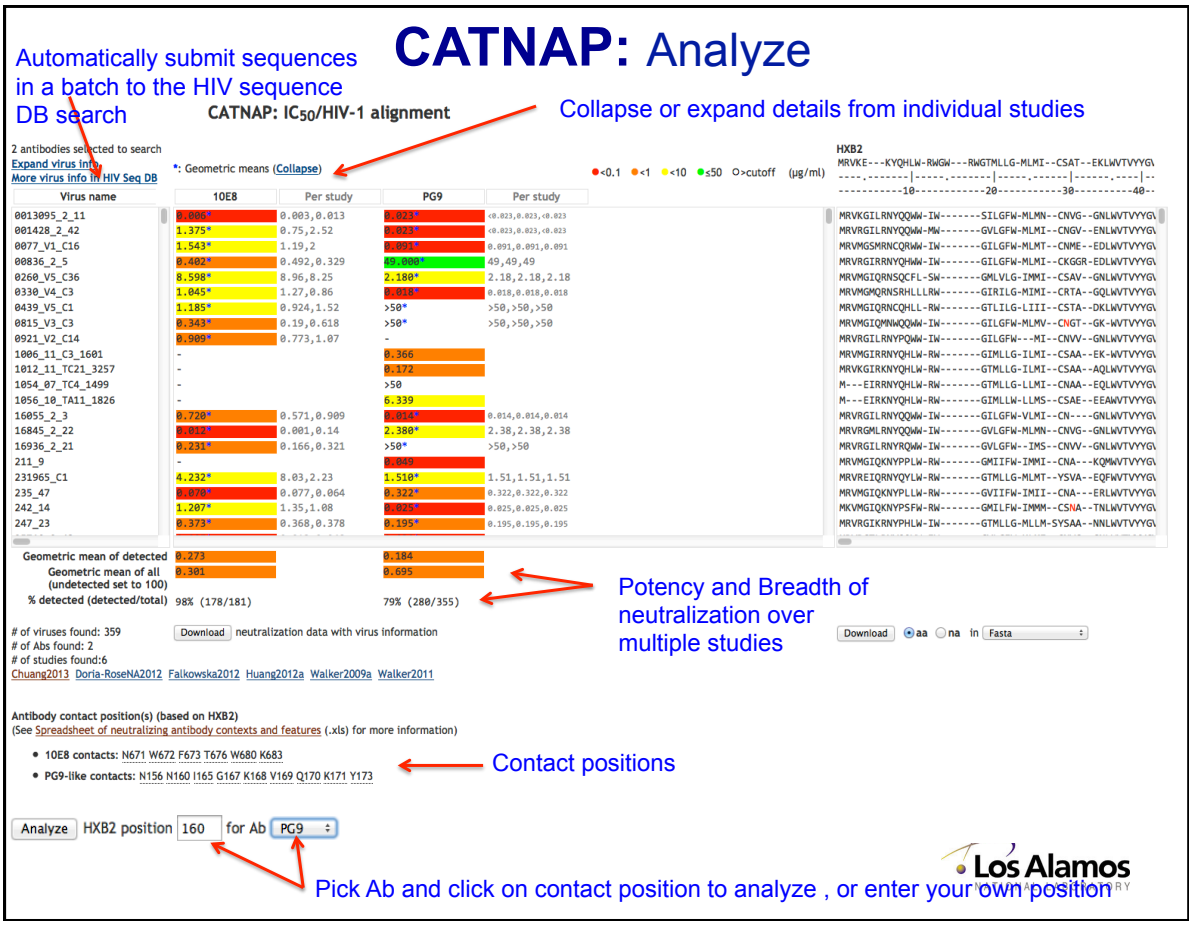
Automatically submit sequences in a batch to the HIV sequence DB search

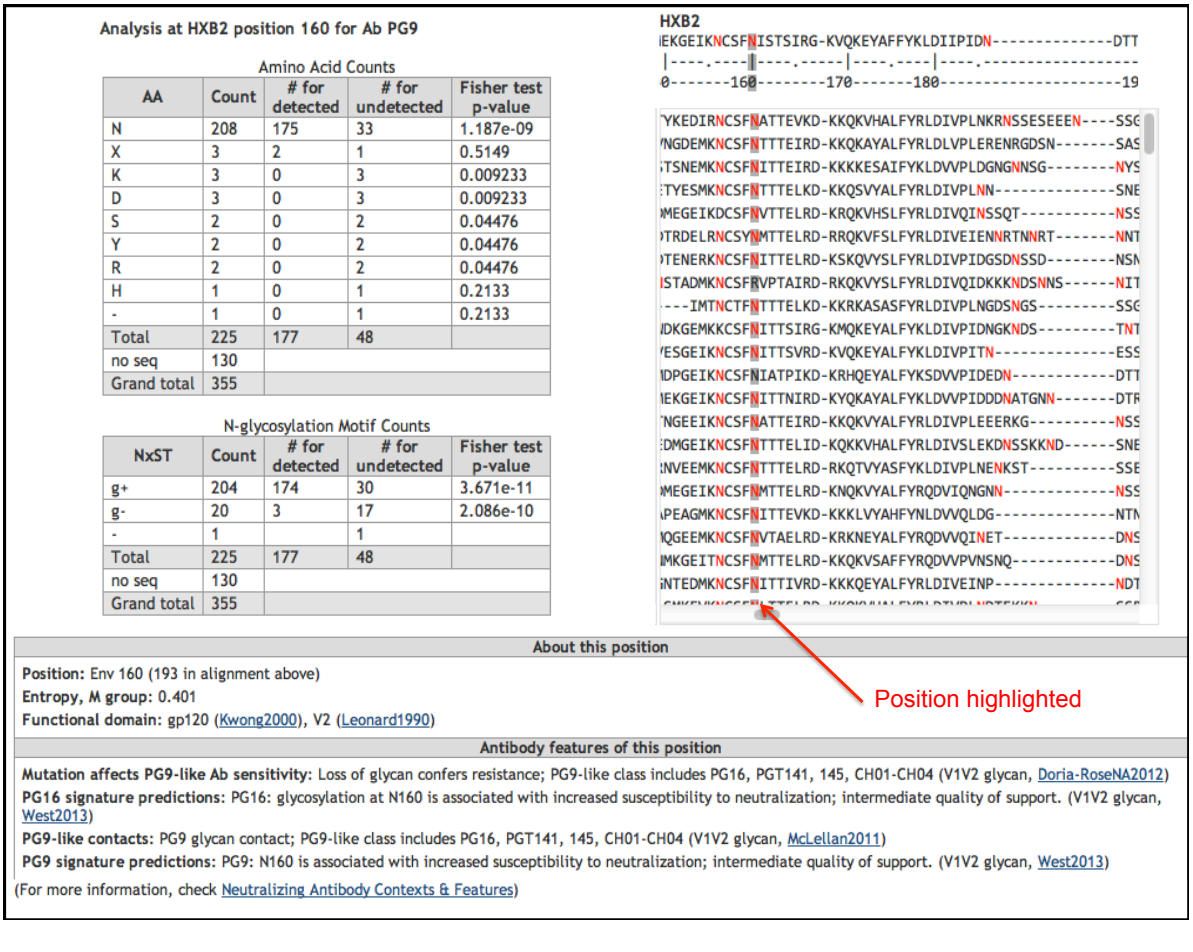
Collapse or expand details from individual studies



Potency and Breadth of neutralization over multiple studies

CATNAP: Analyze





Amino Acid Counts

AA	Count	# for detected	# for undetected	Fisher test p-value
N	208	175	33	1.187e-09
X	3	2	1	0.5149
K	3	0	3	0.009233
D	3	0	3	0.009233
S	2	0	2	0.04476
Y	2	0	2	0.04476
R	2	0	2	0.04476
H	1	0	1	0.2133
-	1	0	1	0.2133
Total	225	177	48	
no seq	130			
Grand total	355			

N-glycosylation Motif Counts

NxST	Count	# for detected	# for undetected	Fisher test p-value
g+	204	174	30	3.671e-11
g-	20	3	17	2.086e-10
-	1		1	
Total	225	177	48	
no seq	130			
Grand total	355			

CATNAP: Ab info

Antibody information

Number of antibodies: 2

Download ◉antibody aa sequences ○antibody na sequences in Fasta

Download table below

Antibody	Structure	Donor	Clonal lineage	Isolation paper	Neutralizing antibody feature	Heavy chain	Light chain
PGT125		Donor 36	PGT128	Walker2011	○ PGT121-123, 125-128, 130 and 131	JN201897 Synthetic construct isolate PGT125 anti-HIV immunoglobulin heavy chain variable region gene, partial cds QSQLQESGPRLVEASETLSLTCNVSGESTGACTYFWGWVRQAPGKGLEWI GSLSHCQSFWGSGWTFHNPSLKSRLTISLDTPKNQVFLKLTSLTAADTAT YYCARFDGEVLVYNHWPKPAWVDLWGRGIPVTVTVSS	JN201914 Homo sapiens isolate PGT125 anti-HIV immunoglobulin light chain variable region mRNA, partial cds QSALTQPPSASGSPGQSITISCNGTATNFVSWYQQFPDKAPKLIIFGVDK RPPGVPDRFSGSRSGTTASLTVSRLQTDDEAVYYCGSLVGNWDVIFGGGT TLTVL
PGT127	○ PGT127 complexed with Man(9)	Donor 36	PGT128	Walker2011	○ PGT121-123, 125-128, 130 and 131 ○ PGT127/ PGT128	JN201899 Homo sapiens isolate PGT127 anti-HIV immunoglobulin heavy chain variable region mRNA, partial cds QPQLQESGPGLVEASETLSLTCTVSGDSTGRCNYFWGWVRQPPGKGLEWI QSLSHCRSYYNTDWTYHNPSLKSRLTISLDTPKNQVFLRLTSVTAADTAT YYCARFGGEVLVYRDWPKPAWVDLWGRGTLVTVSS	JN201916 Homo sapiens isolate PGT127 anti-HIV immunoglobulin light chain variable region mRNA, partial cds QSALTQPPSASGSPGQSITISCTGTSNNFVSWYQQYPGKAPKLVIYEVNK RPSGVPDRFSGSKSGSTASLTVSGLQADDEGVYYCSSLVGNWDVIFGGGT KLTVL

Link to structure in PDB

Description PGT121-123, 125-128, 130 and 131

Antibody class V3 glycan

Reference Walker2011

Type antibody

MAb name PGT121 PGT122 PGT123 PGT125 PGT126 PGT127 PGT128 PGT130 PGT131 (Click MAb name to get to Immunology DB notes)

Env pos.	Feature	AA	Entropy	Annotation
301	gp120, V3 loop	N	0.261	N-linked glycans in positions 332 and/or 301 were important for neutralization by PGT MAbs 125-128, 130, and 131
332	gp120	N	0.904	N-linked glycans in positions 332 and/or 301 were important for neutralization by PGT MAbs 125-128, 130, and 131, this glycan is also critcal for PGT 121-123.

Important position(s) with Hxb2 amino acid: N301 N332

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CATNAP: Virus info

Virus information

Number of viruses: 14

Automatically submit all selected sequences in a batch to the HIV sequence search interface

Download table below

More info in HIV Sequence DB

Virus name	Subtype	Country	Patient health	Days post infection	Days from seroconversion	Fiebig	Risk factor	Accession	Tier	Alias	HIV DB name	Seq data	LANL comments
216_F2_E3_5	A1C	TANZANIA				6	Heterosexual	HM215277			216_F2_E3_5	Yes	
231965_C1	D	UGANDA	acute infection		early	1 or 2		JQ361079	2	231965, 231965_C01	231965_c01	Yes	
231966_C2	D	UGANDA	acute infection		early	1 or 2		JX512899	2	231966_C02	231966_c02	Yes	
234_F1_16_57	C	TANZANIA			early	5	Heterosexual	HM215278			234_F1_16_57	Yes	
235_47	02_AG	CAMEROON				6	Not Recorded	EU513195	2	235	235	Yes	Sequence does not match accession. This sequence/clone was the one used in neutralization studies but it has not yet been deposited in GenBank.
242_14	02A1	CAMEROON				6		EU513188	1B or 2	242	242	Yes	
246_F3_C10_2	AC	TANZANIA				6	Heterosexual	HM215279			246_F3_C10_2	Yes	
246F_C1G	C	ZAMBIA	acute infection		early	2	Heterosexual	FJ496194	2	ZM246, 246F	ZM246F_fID5	Yes	
247_23	DU	CAMEROON					Not Recorded	EU683891	2	247	247	Yes	
249M_B10	C	ZAMBIA	acute infection		early		Heterosexual	EU166862	2	249M	ZM249M_080503_SGA_B10	Yes	
25710_2_43	C	INDIA	acute infection		45	5	Heterosexual	EF117271	1B or 2	25710	HIV_25710_2	Yes	
25711_2_4	C	INDIA	acute infection		45	3	Heterosexual	EF117272	1B or 2	25711	HIV_25711_2	Yes	
25925_2_22	C	INDIA	acute infection		45	3	Heterosexual	EF117273	1B or 2	25925	HIV_25925_2	Yes	
26191_2_48	C	INDIA	acute infection		45	3	Heterosexual	EF117274	2	26191	HIV_26191_2	Yes	

Link to the sequence record in the HIV Sequence DB

CATNAP: Assay info

Assay

Number of antibodies selected: 82 (10-1074, 10-996, 10E8, 12A12, 15e ...)
Number of viruses selected: 14 (216_F2_E3_5, 231965_C1, 231966_C2, 234_F1_16_57, 235_47 ...)
Number of studies selected: 0

Number of data found: 349

Download table below with additional virus info

Hide virus info

Antibody	Virus	Subtype	Tier	Country	Accession	Alias	Reference	IC50	Mean IC50	IC80	Mean IC80
10-1074	231965_C1	D	2	UGANDA	JQ361079	231965_C01, 231965	Mouquet, et al., PNAS 109, E3268 (2012)	>50	>50		
10-1074	231966_C2	D	2	UGANDA	JX512899	231966_C02	Mouquet, et al., PNAS 109, E3268 (2012)	>50	>50		
10-1074	235_47	02_AG	2	CAMEROON	EU513195	235	Mouquet, et al., PNAS 109, E3268 (2012)	0.05	0.050		
10-1074	246F_C1G	C	2	ZAMBIA	FJ496194	246F, ZM246	Mouquet, et al., PNAS 109, E3268 (2012)	0.022	0.022		
10-1074	249M_B10	C	2	ZAMBIA	EU166862	249M	Mouquet, et al., PNAS 109, E3268 (2012)	>50	>50		
10-996	231965_C1	D	2	UGANDA	JQ361079	231965_C01, 231965	Mouquet, et al., PNAS 109, E3268 (2012)	>50	>50		
10-996	231966_C2	D	2	UGANDA	JX512899	231966_C02	Mouquet, et al., PNAS 109, E3268 (2012)	>50	>50		
10-996	235_47	02_AG	2	CAMEROON	EU513195	235	Mouquet, et al., PNAS 109, E3268 (2012)	0.128	0.128		
10-996	246F_C1G	C	2	ZAMBIA	FJ496194	246F, ZM246	Mouquet, et al., PNAS 109, E3268 (2012)	0.092	0.092		
10-996	249M_B10	C	2	ZAMBIA	EU166862	249M	Mouquet, et al., PNAS 109, E3268 (2012)	>50	>50		
10E8	231965_C1	D	2	UGANDA	JQ361079	231965_C01, 231965	Chuang et al. J Virol. 87:10047 (2013)	2.23	4.232		
							Huang, et al., Nature 491, 406 (2012)	8.03			
10E8	235_47	02_AG	2	CAMEROON	EU513195	235	Chuang et al. J Virol. 87:10047 (2013)	0.064	0.070		
							Huang, et al., Nature 491, 406 (2012)	0.077			
10E8	242_14	02A1	1B or 2	CAMEROON	EU513188	242	Chuang et al. J Virol. 87:10047 (2013)	1.08	1.207		
							Huang, et al., Nature 491, 406 (2012)	1.35			

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Neutralization panel: looking forward

- Neutralization data from many more studies, particularly IC80 values.
- Additional measurements of neutralization and antibody binding.
- Alignments of antibody variable domain sequences.
- Signature analysis results using collected data.
- Autologous neutralization data for studies with multiple HIV sequences and multiple antibodies isolated from the same donor.

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ELF

- If you have a peptide that reacts with CD8+ T cells from a person with known HLA type, enter:
  - The peptide that reacts with CD8+ T-cells
  - The HLA type of the person with the reactive CD8+ T cells
- ELF will help identify the possibly reactive epitope by
  - Highlighting appropriate HLA anchor motifs in the peptide
  - Aligning all known epitopes embedded in the peptide from the database to your query sequence, with links to epitope entries
  - Finding potential epitopes based on Immune Epitope Database (IEDB) binding predictions http://www.immuneepitope.org/
- Other useful information provided:
  - Genomic location of your peptide
  - Database records for known CTL epitopes in this region, regardless of HLA.

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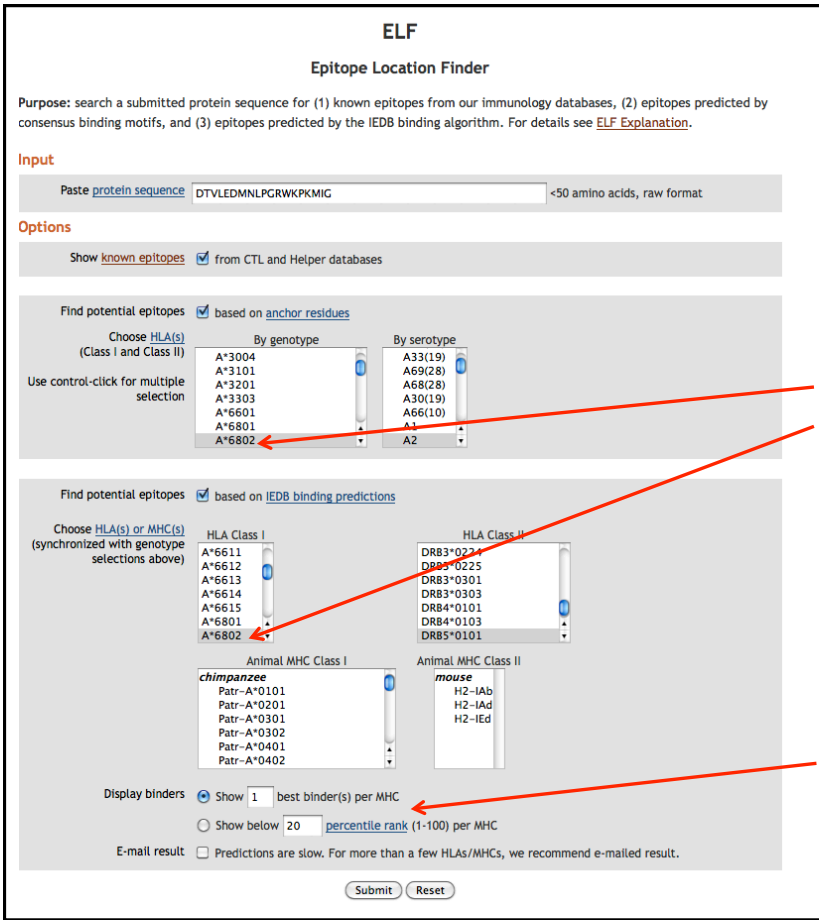

HLA selection is synchronized between 2 analysis options

You can choose how many top binders to show per MHC, or use a binding percentile rank cutoff

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ELF results 1:

Epitopes from our CTL database aligned to your query sequence

Bold red letters indicate residues that differ from the query sequence. The symbol ➤ means the HLA of the epitope matches one of your submitted HLAs. Click on the epitope to see full database entry. Click on "align" to align the epitope to the sequence database via QuickAlign.

Epitopes shown here are completely within the bounds of your query. Epitopes that overlap the ends of your query are included in the "View database records" links above.

Download this alignment in format table

```
DTVLEDMNLPGRWKPKMIG
DTVLEEMNL A*6802   align ➤
DTVLEDINL A*6802   align ➤
DTVLEEWNL A*6802   align ➤
DTVLEEMNL A68      align
DTVLEEMNL A28      align
DTVLEDMNL          align
    EEMNLPGRW B44      align
    EEINLPGKW B44      align
    EEMNLPGRW B*4402   align
    EEMNLPGRW B*4403   align
    EEMNLPGRW B18,B40,B44   align
    EDMNLPGRW          align
    EEMNLPGRW B*44     align
    EEINLPGKW B*4403   align
    EEMNLPGRW          align
        LPGRWKPKMI Cw3     align
        LPGRWKPKMI B7      align
```

Clicking on an epitope takes you to respective CTL or Helper epitope Database entries

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ELF results 2:

Potential epitopes based on anchor residues

These peptides have C-terminal anchor residues, highlighted in **blue**, and internal anchors highlighted in magenta. These anchor residues match one or more motifs associated with the submitted HLA.

Download this alignment in format table

```
DTVLEDMNLPGRWKPKMIG
DTVLEDMNL (A*0205 ........[L])
DTVLEDMNL (A*6802 .[TV]......[VL])
 TVLEDMNLP (A*0206 .[VQ].......)
   LEDMNLPGR (DRB5*0101,DRB5*0101 [FYLM]..[QVIM]....[RK])
```

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ELF results 3:
Potential epitopes based on IEDB database MHC binding predictions, by Alexander Sette's group

Potential epitopes based on IEDB binding predictions

Top binders for each MHC are highlighted in **blue**.
Prediction method: IEDB recommended
Low percentile = good binders
Show up to 1 binder(s) per MHC

Class I

Selected allele(s): A*6802, B*1501

Download this alignment in format table

```
DTVLEDMNLPGRWKPKMIG (Click MHC to see full list of IEDB predictions for that MHC)
     DMNLPGRW       B*1501 (26)
      MNLPGRWK      A*6802 (3.0)
```

Clicking on MHC links to the full list of IEDB predictions for that MHC (see next slide)

Class II

Selected allele(s): DRB5*0101

Download this alignment in format table

```
DTVLEDMNLPGRWKPKMIG (Click MHC to see full list of IEDB predictions for that MHC)
 TVLEDMNLPGRWKPK    DRB5*0101 (17.17)
```

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ELF results 3:
Potential epitopes based on IEDB database MHC binding predictions, by Alexander Sette's group

IEDB Analysis Resource

Home | Help | Example | Reference | Download | Contact

MHC-I binding predictions - Prediction Results

Input Sequences

#	Name	Sequence
1	sequence 1	DTVLEDMNLPGRWKPKMIG

Prediction method: IEDB recommended | Low percentile = good binders
Check to expanded the result: ☐

Allele	#	Start	End	Peptide Length	Sequence	Method used	Percentile Rank
HLA-B*15:01	1	6	13	8	DMNLPGRW	*NetMHCpan*	26
HLA-B*15:01	1	3	13	11	VLEDMNLPGRW	*NetMHCpan*	27
HLA-B*15:01	1	3	11	9	VLEDMNLPG	Consensus (*ANN,SMM,CombLib_Sidney2008*)	27.60
HLA-B*15:01	1	8	17	10	NLPGRWKPKM	*NetMHCpan*	31
HLA-B*15:01	1	7	17	11	MNLPGRWKPKM	*NetMHCpan*	35
HLA-B*15:01	1	2	9	8	TVLEDMNL	*NetMHCpan*	36
HLA-B*15:01	1	2	11	10	TVLEDMNLPG	*NetMHCpan*	47
HLA-B*15:01	1	4	11	8	LEDMNLPG	*NetMHCpan*	48

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Mosaic vaccine tools

Mosaic Vaccine Designer: The Mosaic Vaccine Designer will generate candidate vaccine protein 'cocktails' that optimize coverage of potential T-cell epitopes found in a given background set of protein sequences.

Epitope Coverage Assessment: Alignment independent “n-mer” coverage of sequences by vaccines or peptides.

Positional Epitope Coverage Assessment: Alignment dependent coverage of sequences by vaccines or peptides.

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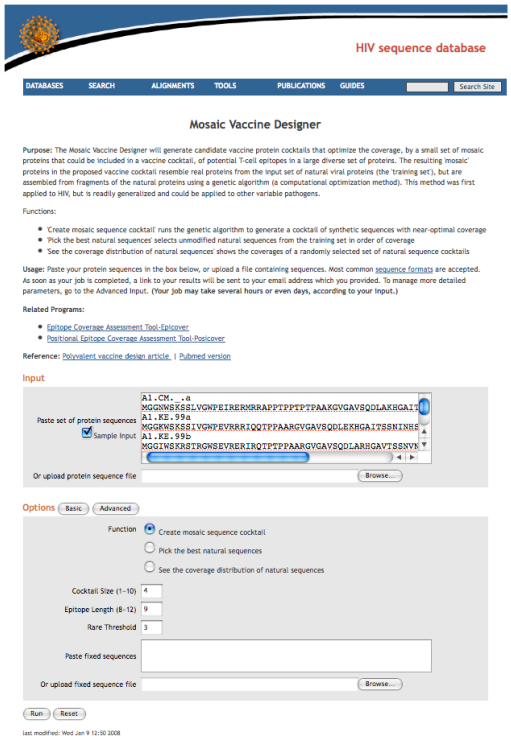
Mosaic Vaccine Designer



Input: protein sequence set for a target population, does not need to be aligned.

Number of mosaic proteins in the set.

Epitope length.

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Epitope Coverage Assessment - Epicover

Input

Use output from MakeVaccine tool

Provide a job number to access output from the Mosaic Vaccine Designer tool:

OR

Provide input sequences

Paste antigen protein sequence(s): [Sample Input]

upload more [+] antigen sequence files

and/or upload as files: Browse...

Paste test set protein sequences:

upload more [+] test sequence files

and/or upload as files: Browse...

Options

Send results as an email instead of displaying in browser (useful in case of a browser time-out):

Nominal epitope length: 9

Maximum amino acid mismatches to score (range from 0): 2

Minimum number of occurrences of a potential epitope in viral protein set to consider for coverage: 3

Precision to use when reporting coverage: 4 decimal places

Advanced Options

Upload file of grouped sequence names: Browse...

Report on subsets defined according to first character(s) in sequence names

Submit Reset

Input:
Vaccine set
Test set

Can report on subsets defined according to the first several characters in sequence names or user-defined subsets

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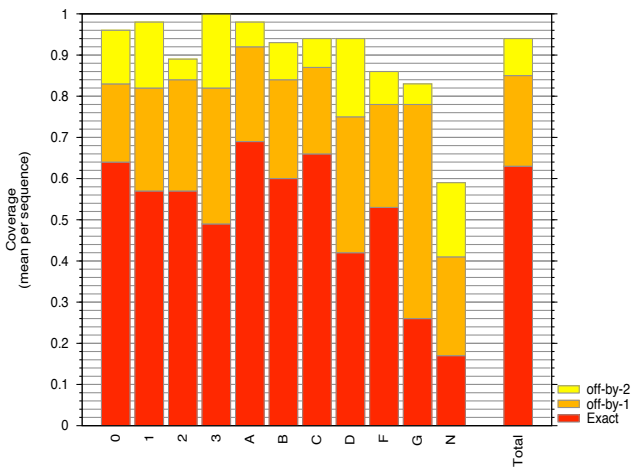
Epicover output

vaccine set	subset	subset count	Off-by-0	Off-by-1	Off-by-2	rare(<3,>1)	unique	absent
vaccine_set_from_user	**Total**	**63**	**0.6615**	**0.8914**	**0.9660**	**104**	**114**	**334**
vaccine_set_from_user	A	11	0.7232	0.9429	0.9935	47	36	334
vaccine_set_from_user	B	11	0.6378	0.8845	0.9755	25	19	334
vaccine_set_from_user	C	35	0.6921	0.8994	0.9637	51	45	334
vaccine_set_from_user	D	4	0.4217	0.7546	0.9443	4	9	334
vaccine_set_from_user	F	1	0.5300	0.7800	0.8600	4	5	334
vaccine_set_from_user	G	1	0.2597	0.7792	0.8312	0	0	334



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Positional Epitope Coverage Assessment - Posicover

Provide a job # from Mosaic Vaccine Designer:
(Only the antigen set is used. Provide the ALIGNED viral test set below)
AND/OR
Paste antigen protein set or peptide cocktail: (alignment not required) [Sample Input]
upload more [+] antigen files
and/or upload antigen file(s): Browse...

Test set proteins

Paste **ALIGNED** test viral protein set: [Sample Input]
or upload an **ALIGNED** test proteins file: Browse...

Input:

Vaccine set
ALIGNED test set

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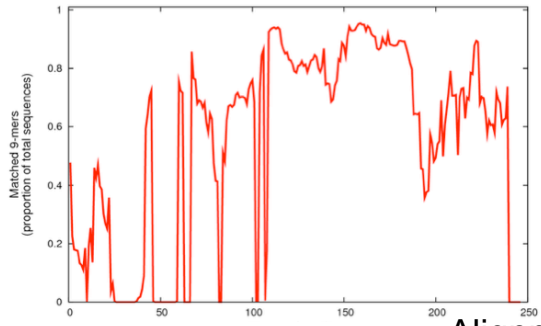
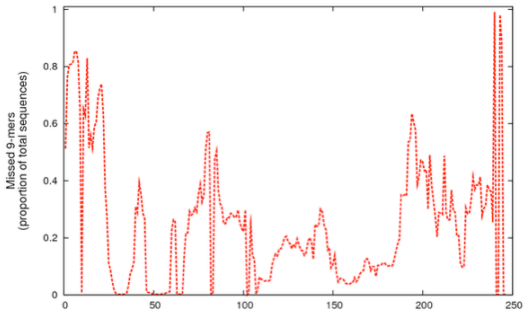
Examples of Posicover outputs

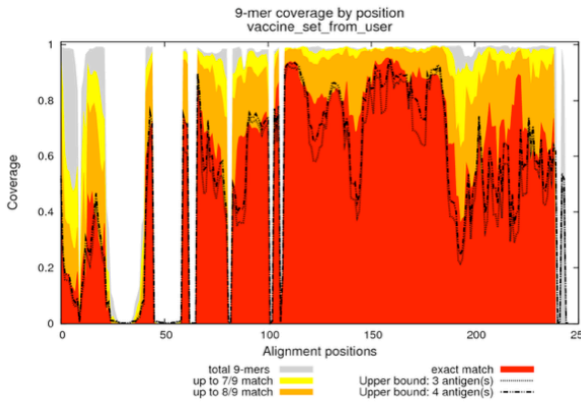
Matched 9-mers

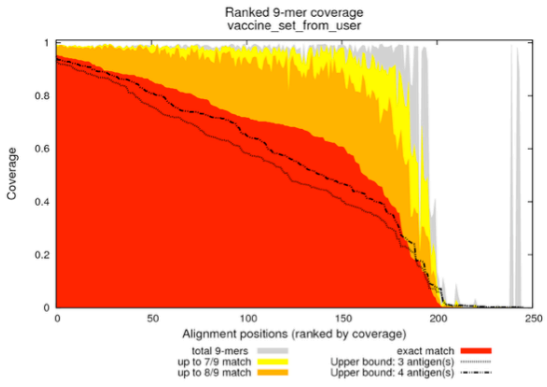


Missed 9-mers



Alignment positions





Examples of Posicover outputs

User's sequence alignment:

Each aa is represented as a single-colored square

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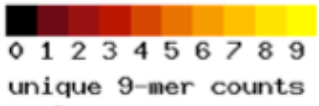
Examples of Posicover outputs

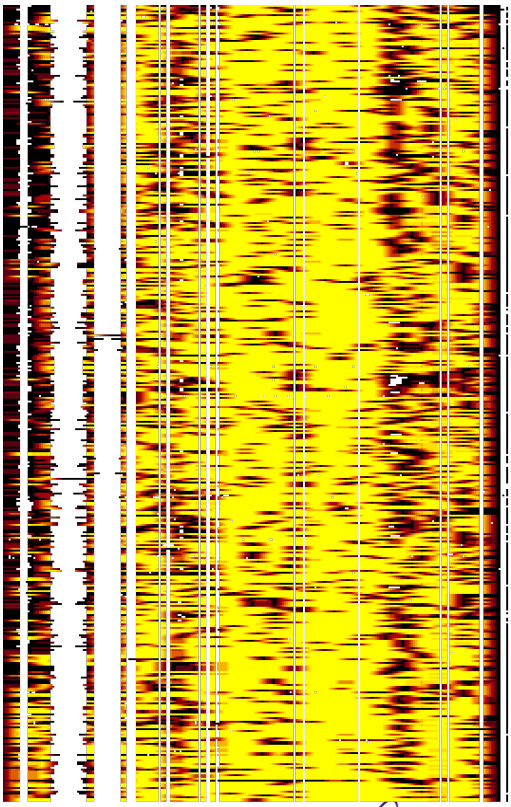
Each amino acid is colored according to the set of 9-mers that contain it:

Yellow: all 9-mers that overlap with amino acid are perfectly matched in a test vaccine set;

Increasingly red: fewer and fewer matches in the overlapping set of 9-mers that span the amino acid;

Black: amino-acid residues that are not included in any vaccine set





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Please leave any comments or suggestions with us:

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